

Attorney Docket No. P66036US1
Appln. No. 09/750,185

Remarks/Arguments:

As an initial matter the Office Action incorrectly indicates that there were at the time 250 total claims of record and that claims 119-250 were pending. As correctly indicated in the previous Office Action, mailed February 25, 2003 (paper no. 12), there were only 236 total claims at the time, with claims 119-236 pending; i.e., claims 119-236 added by amendment filed May 14, 2001. Correction of the record is requested accordingly.

Claims 237-278, presented hereby, are pending.

Claims 119-236 are cancelled hereby, without prejudice or disclaimer.

Pursuant to the requirement for election of species, and in accordance with the suggestions of the examiner as written in the Office Action, the presented claims represent the subject matter of elected claims 213-231 amended in such a way that they fall within the scope of the elected species. Non-elected claims 119-212 and 232-236 are cancelled.

After carefully studying the Office Action, in particularly the allegations of indefinite claim language and the prior art allegedly anticipating the claimed invention, it seems to the applicant that the Office Action reflects a possible misinterpretation the subject matter claimed. In order to more clearly define the invention, therefore, applicant has revised the language of claims 213-231, which revised language appears in presented claims 237-278.

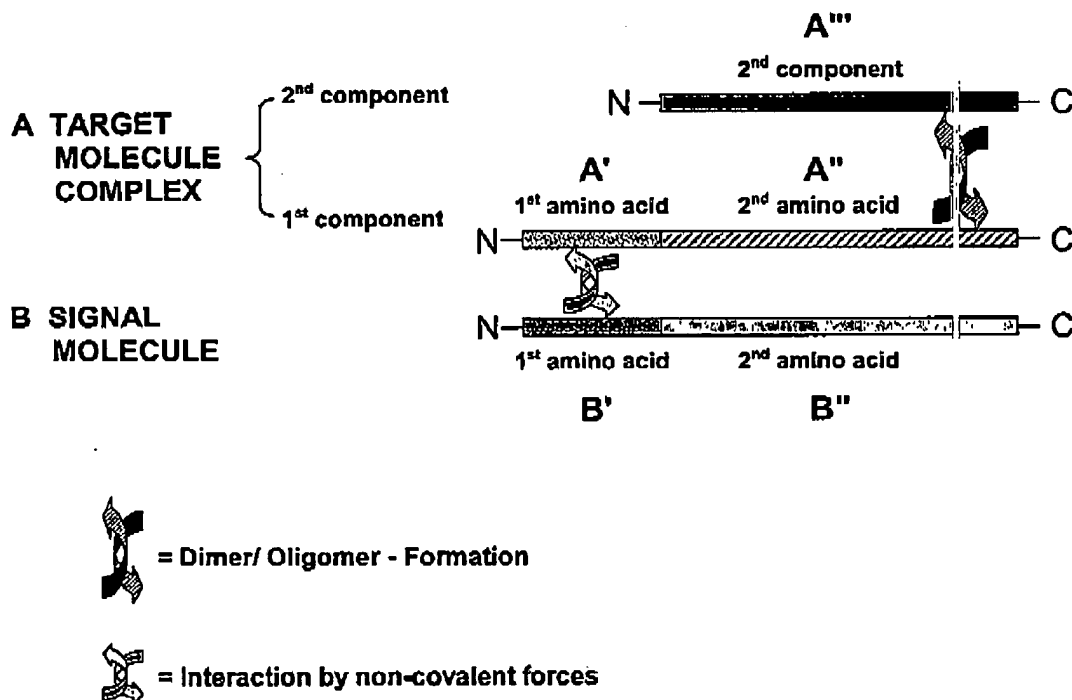
The original claim language and the fundamental concept of the instant invention relates to target molecules comprising a first and a second amino acid sequence and signal molecules comprising a first and a second amino acid sequence. The elected species 'retroviral capsid protein'

Attorney Docket No. P66036US1
 Appln. No. 09/750,185

corresponds to a second amino acid sequence of a signal molecule. The elected species 'receptor' corresponds to a second amino acid sequence of a target molecule. Thus, both cases of the elected species are related to second amino acid sequences of either a signal or a target molecule.

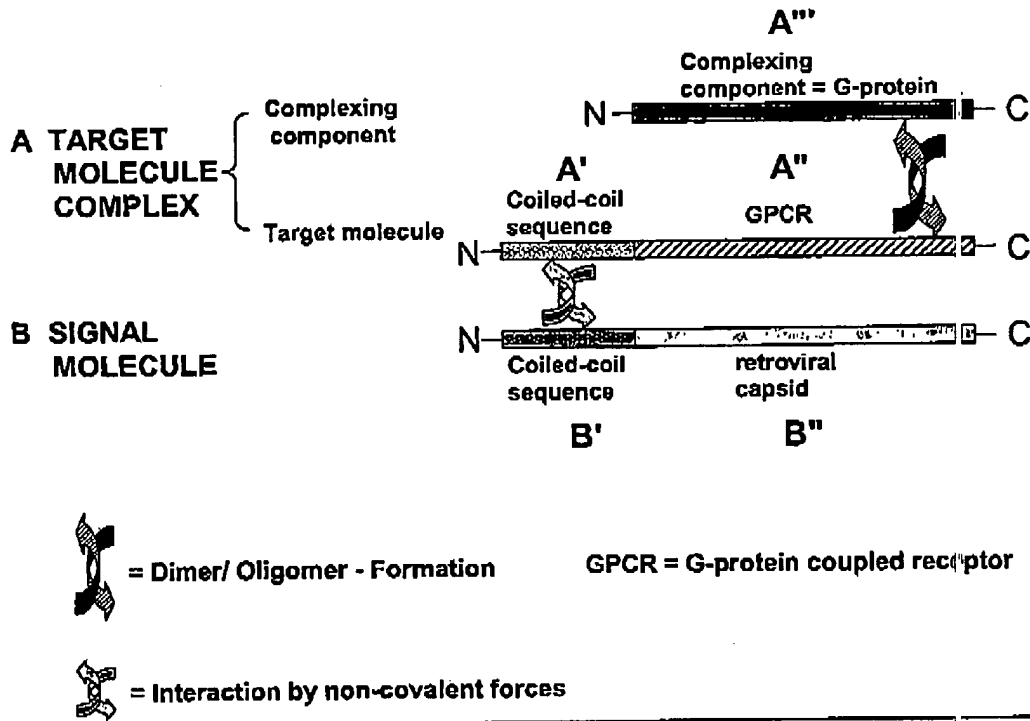
As an illustrative aid in the following discussion of the invention, schematic drawings are provided in Figs. 1 and 2, below. Figures 1 and 2 illustrate, schematically, the wording used in the claims as originally filed (Fig. 1) compared with that used in the present claims (Fig. 2).

Fig. 1
Original Claims



Attorney Docket No. P66036US1
 Appln. No. 09/750,185

Fig. 2
Present (Amended) Claims



The fundamental concept that forms the basis of invention disclosed and claimed in the subject application includes the use and production of target-molecule complexes.

As illustrated In Fig. 2, feature **A''**, the "G-protein coupled receptor," or GPCR (in the original claims the "second amino acid sequence of the second component"), differs from feature **B''**, the "retroviral capsid sequence" (in the original claims the "second amino acid sequence of the signal molecule"). As further illustrated, feature **A'**, the "coiled-coil sequence" (in the original claims the

Attorney Docket No. P66036US1
Appl. No. 09/750,185

"first amino acid sequence of the second component"), typically differs from feature B', the "coiled-coil sequence" (in the original claims the "first amino acid sequence of the signal molecule"). Additionally, the coiled-coil sequence "A'" is different than the "retroviral capsid sequence" A" (correspondingly, as recited in the original claims, the "first amino acid sequence of the signal molecule" is different than "second amino acid sequence").

The wording "coiled-coil sequence" in the present claims represents subject matter identical to that represented in the original claims by the wording "first amino acid sequence of either a signal molecule or a first component". The wording "G-protein coupled receptor" in the present claims represents subject matter identical to that represented in the original claims by the wording "second amino acid sequence of a first component". The wording "retroviral capsid sequence" in the present claims represents subject matter identical to that represented in the original claims by the wording "second amino acid sequence of a signal molecule". The wording "target molecule" in the present claims represents subject matter identical to that represented in the original claims by the wording "first component". The wording "complexing component" in the present claims represents subject matter identical to that represented in the original claims by the wording "second component or components".

In accordance with the claimed invention, the "complexing component", i.e., a G-protein, physically interacts with the "G-protein coupled receptor," such that they form hetero-dimers or hetero-oligomers and, thus, are associated in a "target molecule complex".

Attorney Docket No. P66036US1
Appl. No. 09/750,185

Terminology in the present claims consistent with that in the original claims include "target molecule complex" and "signal molecule".

All of the replacement terms used in the present claims are supported, explicitly and implicitly, in the subject application as originally filed.

Note should be taken that Figs. 1 and 2, above, are provided for illustrative purposes only, and neither the figures nor the accompanying discussion is to be interpreted as a limit on the scope of the application disclosure or the subject matter claimed in any way.

Claims 213 to 231 were rejected under 35 USC 112, ¶2, for allegedly being indefinite. Reconsideration is requested.

The statement of rejection alleges that claims 213-231 are indefinite and confusing with respect to the use of the terms "first amino acid and second amino acid sequence of a first component", a "target molecule complex of a first component", a "target molecule of a second component", the "first and second amino acid sequence of a signal molecule", and with respect to the relationship between each sequences constituting a virus like particle as described in the instant invention.

Applicant submits that the language reflected in the present claims avoids any potential for confusion as to the subject matter claimed. Careful consideration is therefore requested in light of the amended wording appearing in the present claims. For the examiner's convenience, applicant provides, as follows, the location in the text of the instant application where "target molecules", "signal molecules", "target molecule complexes" and "first and second component" are defined:

Attorney Docket No. P66036US1
Appln. No. 09/750,185

On pages 4, 5, 14 and 15, 58 and 75 of the subject application as filed, "target molecules" are described as functional proteinaceous molecules, which are heterologous to a virus or virus like particle, i.e., they are naturally not occurring in viruses or virus like particles. According to the claimed invention, said "target molecules" are incorporated/encapsulated into virus like particles. "Target molecules" are composed of two fused amino acid sequences, which confer to a "target molecule" specific properties. One of said two amino acid sequences of a "target molecule", the "coiled-coil sequence" (in the original claims the "first amino acid sequence of the first component of the target molecule complex"), interacts specifically, in a non-covalent manner, with a "coiled-coil sequence" of a "signal molecule" (in the original claims a "first amino acid sequence of a signal molecule"). The other of said two amino acid sequences, the "G-protein coupled receptor" of the "target molecule" (in the original claims the "second amino acid sequence of the first component of the target molecule complex") confers to the "target molecule" the characteristics of a functional proteinaceous molecule, e.g. of a receptor.

On pages 4, 5, 6, 58 and 75 of the subject application as filed, "signal molecules" are precisely described. Signal molecules, as used in the instant application, are composed of two fused amino acid sequences, which confer to the signal molecule specific properties. One of said two amino acid sequences, the "coiled-coil sequence" (in the original claims the "first amino acid sequence of said signal molecule"), interacts specifically, in a non-covalent manner, with a "coiled-coil sequence" of a target molecule (in the original claims a "first

Attorney Docket No. P66036US1
Appln. No. 09/750,185

amino acid sequence of the first component of the target molecule complex "). The other of said two amino acid sequences, the "retroviral capsid sequence" encoding a retroviral capsid protein (in the original claims the "second amino acid sequence of said signal molecule"), confers on the signal molecule the ability to assemble into virus like particles. The molecule referred to as "signal molecule" is defined by a distinct and specific functional property, i.e., the property of inducing an assembly of virus like particles.

The examples illustrated in figure 25 on page 72 and pages 18, 50 and 51 of the subject application as filed, describe in detail the use and production of target molecule complexes, and the meaning of the terms "target molecule complex" and "complexing component or components" and how they are related to each other. (For additional explanation, see the illustrations and comments, above, in connection with the requirement for election of species.)

The practical benefit of using and/or producing target molecule complexes is to operate with whole functional complexes of target molecules. Such functional complexes consist of two or more subunits which, together by a process of physical association, form a functional unit. This complex as a whole may gain new, or additional, or enhanced functions, or due to the complex-formation of individual units or components, may acquire additional or enhanced functions. On page 50 of the subject application, several examples for such target molecule complexes are given. The G-protein coupled receptors (GPCRs), for instance, are interacting intracellularly with so called G-proteins to form a complex, hence capable to carry out specific functions of signaling processes. In the instant

Attorney Docket No. P66036US1
Appl. No. 09/750,185

invention, target molecule complex formation with respect to GPCRs is disclosed in detail and is inter alia exemplified for the human endothelin A receptor. In this example, the "target molecule" (in the original claims the "first component of a target molecule complex") is the tagged human endothelin A receptor. Since the "target molecule" comprises the endothelin A receptor sequence and the "coiled-coil sequence", it will be able to interact with the "coiled-coil sequence" of the signal molecule. In addition, the endothelin A receptor sequence of the target molecule will be able to associate with a "complexing component" (in the original claims "second component"), for instance, the alpha G-protein subunit (Gs-alpha). Such a "complexing component" may be endogenously present within the host cell used, as is the case for the alpha G-protein (refer to page 51 and Figure 25 of instant invention as filed), or it will be additionally co-expressed within the same cell. The "complexing component" does not interact with the "signal molecule" because said complexing component, i.e., the G-protein, is chosen in such a way that it will associate with the respective receptor, i.e., the G-protein coupled receptor, in a self-acting manner.

The statement of rejection maintains that claims 218, 226, 227 and 230 are allegedly indefinite due the recitation of "fragments" and "derivatives." According to the statement of rejection, the claims are rendered indefinite because definitions for "fragments" and "derivatives" are (allegedly) not provided in the subject application.

The correct test for indefinite claim language is whether one of ordinary skill in the art would be confused as to the meaning of subject matter defined by the language at issue. *In re Kroekel*, 183

Attorney Docket No. P66036US1
Appln. No. 09/750,185

USPQ 610 (CCPA 1974). Applying this test demonstrates that the language at issue satisfies the requirements of 35 USC 112, ¶2.

The usage of the wording "fragments" and "derivatives" is common practice and their meanings are well known to the person skilled in the art. It must be remembered that, while claims are to be given their broadest reasonable interpretation during prosecution, the definition of a claim limitation given by the Examiner cannot be different than would be given by one of ordinary skill in the art. *In re Cortright*, 49 USPQ2d 1464 (Fed. Cir. 1999). Moreover, merely that it requires some thought to understand the meaning of a claim term does not render the term indefinite under §112, ¶2. *S3 Inc. v. nVIDIA Corp.*, 59 USPQ2d 1745, 1748 (Fed. Cir. 2001).

The term "fragment" as used in the present claims would be readily understood by the skilled artisan to include, for example, an alternatively spliced, truncated, or otherwise cleaved translation product. The term "derivative" would be readily understood to refer to a mutated, chemically modified, or otherwise altered translation product. For instance, a "derivative" may be generated by processes such as altered phosphorylation, or glycosylation, or acetylation, or lipidation, or by altered signal peptide cleavage or other types of maturation cleavage. These processes may occur post-translationally. Further, a "derivative" refers to any polypeptide or protein disclosed in the present invention in which one or more amino acids are added and/or substituted and/or deleted and/or inserted at the N-terminus, and/or the C-terminus, and/or within the native amino acid sequences of the native polypeptides or proteins. This shall include any shorter or longer version of a polypeptide or protein, as well as proteins and polypeptides which can be isolated from nature or

Attorney Docket No. P66036US1
Appln. No. 09/750,185

be produced by recombinant and/or synthetic means. Native proteins or polypeptides refer to naturally-occurring truncated or secreted forms, naturally occurring variant forms (e.g. splice-variants) and naturally occurring allelic variants.

With reference to the definition of "fragment" given above, attention is directed to the functionality of the recited "fragments," on the one hand, with that of the complete signal molecule, on the other. The recited "fragments" of a signal molecule retain the capacity to initiate at least the incorporation/encapsulation; in other words, to confer on the signal molecule the ability to assemble into virus-like particles. The precise amino acid sequence results from the given amino acid sequence of a virus capsid or virus particle like capsid protein, as explained elsewhere, herein.

Merely that it requires some thought to understand the meaning of a claim term does not render the term indefinite under §112, ¶2.

The purpose of the claims is not to explain the technology or how it works, but to state the legal boundaries of the patent grant. A claim is not "indefinite" simply because it is hard to understand when viewed without benefit of the specification.

S3 Inc. v. nVIDIA Corp., 59 USPQ2d 1745, 1748 (Fed. Cir. 2001). Moreover, while claims are to be given their broadest reasonable interpretation during prosecution, the definition of a claim limitation given by the Examiner cannot be different than would be given by one of ordinary skill in the art. *In re Cortright*, 49 USPQ2d 1464 (Fed. Cir. 1999).

To the extent the rejection concerns the scope of the claim terms at issue, the fact that the terms are generic (broad) has no bearing on whether the claims are indefinite under §112, ¶2, since claim "breadth is not to be equated with indefiniteness." *In re Miller*, 169 USPQ 547, 600 (CCPA

Attorney Docket No. P66036US1
Appl. No. 09/750,185

1970). Although an "undoubtedly large number" of embodiments might fall within the scope of a generic expression "the expression is not for that reason indefinite," *In re Skoll*, 187 USPQ 481, 482 (CCPA 1975), and whether a particular embodiment is covered by the expression "is rendered no less certain by the large number."

In ¶s "9" and "10" of the §112, ¶2, rejection, according to the statement of rejection claim 1 (119?) and claim 225 are allegedly incomplete for omitting allegedly essential steps. The omitted steps concern "how" to perform the steps recited in each of the rejected claims. As such, the statement of rejection confuses the function of the claims, on the one hand, with the function of the specification, on the other; *how* the invention is to be practiced is the function of the specification, not the claims, the function of the claims being to define the legal limits of the invention. *In re Roberts*, 176 USPQ 313, 315 (CCPA 1973).

The allegations of "omitting essential steps" fail to support the rejection under §112, ¶2, since "it is not necessary that a claim recite each and every element needed for the *practical utilization* of the claimed subject matter." *Bendix Corp. v. United States*, 204 USPQ 617, 621 (Ct. Cl. 1979) (*emphasis added*). *Carl Zeiss Stiftung v. Renishaw PLC*, 20 USPQ2d 1094, 1101 (Fed. Cir. 1991) (following *Bendix Corp.*).

Moreover, a patent applicant has the prerogative of claiming "less than the entire invention." *Andrew Corp. v. Gabriel Electronics, Inc.*, 6 USPQ2d 2010, 2014 (Fed. Cir. 1988). A "patentee may claim the whole or only part of his invention." *McLain v. Ortmayer*, 141 U.S. 419, 423-24 (1891).

Attorney Docket No. P66036US1
Appln. No. 09/750,185

Claims 213 to 231 were rejected under 35 USC 112, ¶1, for allegedly lacking enablement. Reconsideration is requested.

Lack of enablement is not demonstrated merely because the claim scope might, theoretically, cover embodiments that do not work; the function of the claims is not to specifically exclude possibly inoperative embodiments. *Atlas Powder v. E.I. du Pont de Nemours Co.*, 224 USPQ 409 (Fed. Cir. 1984). Lack of enablement under §112 is not established by mere allegations of undue breadth, that is, by merely arguing that claims read on non-disclosed embodiments. *Horton v. Stevens*, 7 USPQ2d 1245 (BPA & I 1988).

In order to satisfy the requirements of §112, first paragraph, "it is not necessary to embrace in the claims or describe in the specification all possible forms in which the claimed principle may be reduced to practice." *Smith v. Snow*, 294 U.S. 1, 11 (1935). The law does not require an applicant to describe in his specification every conceivable embodiment of the invention. *SRI Int'l v. Matsushita Elec. Corp. of America*, 227 USPQ 577, 586 (Fed. Cir. 1985). Moreover, while working examples drawn to specific embodiments may be desirable, they are not *required* in order to satisfy enablement under §112. *In re Strahilevitz*, 212 USPQ 561 (CCPA 1982). It is well established that working examples are not necessary when one possessed of knowledge of ordinary skill in the art could practice the invention without the exercise of undue experimentation. *Ex parte Nardi*, 229 USPQ 79 (BPA & I 1986).

Enablement under § 112 of the statute is determined from the viewpoint of one of ordinary skill in the art at the time of filing the application for patent, i.e., at the time of constructive reduction

Attorney Docket No. P66036US1
Appl. No. 09/750,185

to practice. The person of ordinary skill in the art brings with him a knowledge and understanding of the entirety of the prior art up until the date of application.

Since the skilled artisan is well aware of what is already known in the art, providing the same information in a patent specification would be redundant. In "satisfying the enablement requirement, an application need not teach, and preferably omits, that which is well known in the art." *Staehelin v. Secher*, 24 USPQ2d 1513, 1516 (BPA&I 1992). A "patent need not disclose, and preferably omits, that which is well known in the art." *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81, 94 (Fed. Cir. 1986).

The question of how the target molecules are constructed and of how the first and the second amino acid sequence of either target molecules or signal molecules will be linked is answered by the description and examples of the application. A detailed description of a "target molecule" and a "signal molecule" is provided, herein. Target molecules and signal molecules comprise sequences as listed in materials and methods, on pages 75 and 76, of the subject application as filed. The selection of the retroviral capsid sequence of the signal molecule is exemplified by the given retrovirus gag-gene sequences, as referenced in public literature and patent applications listed on page 6 of the subject application. A person skilled in the art will, without undue experimentation, use listed references and public genomic databases to obtain signal molecule sequences to work with. Further, a full description of prior art in terms of the gag-gene and protein is given on page 9 to 13 of the subject application application. The selection of the G-protein coupled receptor sequence of

Attorney Docket No. P66036US1
Appln. No. 09/750,185

the target molecule is determined by given GPCR gene sequences encoding functional proteinaceous molecules.

The construction, i.e., fusion of the first amino acid sequences and the second amino acid sequences of either target molecules or signal molecules, respectively, is sufficiently described in the material and methods section of the application as filed on pages 75 and 76 of The subject application. Techniques for creating such constructs are per se known methods, i.e., cloning strategies, known to those of ordinary skill in the art and are commonly available from state-of-the-art literature, as for example the handbook of Sambrook and Russell, *Molecular Cloning: A Laboratory Manual* (and periodic updates thereof), Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York, 1989.

The question of how to functionally operate the first amino acid sequences, i.e., in amended terms the coiled-coil sequences, of signal molecules and of target molecules, respectively, is sufficiently described in the following example: The non-covalent interaction of the first amino acid sequences, i.e., the K-coil sequence and the E-coil sequence, as indicated on pages 75 and 76 of the invention as filed, is based on their intrinsic properties and on their structural characteristics (for reference see Tripet et al., *Protein Engineering* 1996, 9: 1029-1042). These characteristics (e.g. electrostatic interactions, hydrophobic packaging, chain length and orientation, specificity, stability and oligomerization state) control the formation of a highly specific and stable two-stranded α -helical coiled-coil protein motif. The coiled-coil dimerization domain consists of five repeating heptads (E-coil and K-coil amino acid sequences), which is reported to be the optimal length for the

Attorney Docket No. P66036US1
Appln. No. 09/750,185

formation and the stability of such a coiled-coil structure. Hydrophobic amino acid residues within these peptides, i.e., valine and leucine, create amphipathic helices, which in combination with the electrostatic interactions and interhelical ionic interactions drive the folding and stability of the coiled-coil structure. The heterodimerization between the two oppositely charged E-coil and K-coil strands is electrostatically preferred.

Thus, in this example the general concept behind the non-covalent interaction between the first amino acid sequences, i.e., the coiled-coil sequences, of target molecule and signal molecule is based on the selective α -helical coiled-coil heterodimer formation and relies on the creation of receptor, i.e., a GPCR, fused to one of the two described coiled-coil strands, and the creation of a retroviral capsid sequence fused to the other oppositely charged coiled-coil strand. The production of such fusion proteins, the target molecule and the signal molecule, is sufficiently described by the applicant. Since the non-covalent functional operation is a self-acting process, it results from the use of both fusion proteins in, for instance, a cell.

As aforementioned, the non-covalent functional operation is a self-acting process, driven by a variety of forces, which are listed in the instant invention and in the section above. These interactive forces are due to the very specific intrinsic physico-chemical properties of both peptide sequences used, for details please refer to Tripet et al., Protein Engineering 1996, 9: 1029-1042. The peptides of the present invention, the first amino acid sequences, i.e., the coiled-coil sequences of either a target or a signal molecule, such as E-coil and K-coil strands, are oppositely charged. Owing to these properties they tend to form a heterodimeric α -helical coiled-coil structure. Bringing both

Attorney Docket No. P66036US1
Appln. No. 09/750,185

peptides close together, e.g. by means of coexpression in a host cell, ensures a non-covalent interaction between them. As E-coil and K-coil strands are fused to the second amino acid sequences, i.e., in amended terms the G-protein coupled receptor and the retroviral capsid sequence, of either a target and a signal molecule, respectively, and because both strands are interacting with each other, a complex will be formed which is composed of the signal molecule and the target molecule.

The statement of rejection maintains that claim 225 is incomplete in lacking the step of measuring the binding constant K_{ass} between signal molecule and target molecule. The applicant is considering that there is no need for measuring the binding constant between target molecules and signal molecules, as an in-depth analysis of the binding characteristics (rate of K_{ass} , K_{diss} and K_d) of the peptides of the instant invention, i.e., E-coil and K-coil, is given by Tripet et al., Protein Engineering 1996, 9: 1029-1042. As E-coil and K-coil, i.e., the first respective amino acid sequences, i.e., the coiled-coil sequences, of the target molecule and the signal molecule, are the driving forces for the interaction, i.e., for binding of the molecules as a whole, their binding constant largely reflects the whole interaction between signal molecules and target molecules.

Claims were rejected under 35 USC 102(b) for allegedly lacking novelty and under 25 USC 103(a) for alleged obviousness. Reconsideration of the aforesaid rejections under §102(b) and §103(a) is requested.

For anticipation under § 102 to exist, each and every claim limitation, as arranged in the claim, must be found in a single prior art reference. *Jamesbury Corp. v. Litton Industrial Products*,

Attorney Docket No. P66036US1
Appln. No. 09/750,185

Inc., 225 USPQ 253 (Fed. Cir. 1985). The absence from a prior art reference of a single claim limitation negates anticipation. *Kolster Speedsteel A B v. Crucible Inc.*, 230 USPQ 81 (Fed. Cir. 1986). A reference that discloses "substantially the same invention" is not an anticipation. *Jamesbury Corp.* To anticipate the claim, each claim limitation must "*identically* appear" in the reference disclosure. *Gechter v. Davidson*, 43 USPQ2d 1030, 1032 (Fed. Cir. 1997) (*emphasis added*). To be novelty defeating, a reference must put the public in possession of the identical invention claimed. *In re Donahue*, 226 USPQ 619 (Fed. Cir. 1985).

As explained below, with particular reference to present independent claims 237, 251, and 265, the subject matter of the present claims is not anticipated by any of the references relied on to reject the claims.

The statement of rejection considers claims 213, 215-223, 226-229, and 231 to be anticipated based on any of Schubert et al., *J. Virology*, 66, 1992, 1579-1589, Van Es et al. (EP 0960,942A2), Kingsman et al. (WO 88/03563A1), and Gowans et al. (WO 98/28004A1).

Schubert shows what kind of structural features are required in the particular disclosed example for the efficient insertion of a foreign membrane protein into the envelope of a virus particle. The reference describes working with the vesicular stomatitis virus (VSV), which belongs to the group of rhabdoviridae, and focused on the envelope protein of this virus and on the insertion of the human HIV-receptor (CD4). It shows the insertion of a foreign glycoprotein, i.e., a functional chimeric HIV-receptor (CD4/G) and a normal HIV-receptor (CD4), into the VSV envelope. The

Attorney Docket No. P66036US1
Appln. No. 09/750,185

efficient transport, the sorting of the glycoproteins during the process of virus assembly, and the VSV particle formation depends on the coexpression of VSV env proteins.

In contrast to the approach of the present invention, Schubert and coworkers expressed the wild-type env-glycoprotein G as a chimeric gene in a vaccinia virus. They did not use a retroviral system. Thus, a retroviral system as in instant invention is not anticipated. Only a part of the CD4 HIV-receptor was fused to only the cytodomain of the G protein. The CD4 HIV-receptor may be considered as a target molecule, but it is not a receptor in the common sense, because CD4 is a molecule, which serves as a receptor for HIV viruses, thus it functions like a cell-adhesion molecule, a molecule where viruses may dock to, but this docking does not activate a signal transduction cascade within the cell as it is the case for a "receptor" in the common sense. Thus, a receptor as a target molecule as described in the instant invention is not anticipated by Schubert et al.. The env-glycoprotein G is not a capsid protein, as it is an integral membrane protein of the viral envelope, an envelope protein. Thus, a signal molecule, comprising a retroviral capsid sequence as disclosed in the present invention, is not anticipated. Furthermore, in the study from Schubert et al., a fusion protein of a HIV-receptor and the env-glycoprotein is generated, i.e., according to the statement of rejection, a fusion product between a target and a signal, which is based on a covalent bond. The target molecule and signal molecule of the instant invention differ from those described by Schubert et al., as they interact with each other in a non-covalent manner. Even if Schubert and coworkers coexpressed said covalently linked fusion product with a vaccinia virus recombinant, expressing the complete HIV envelope protein, the two coexpressed molecules are separate proteins,

Attorney Docket No. P66036US1
Appl. No. 09/750,185

coexisting within the infected cell, they are neither covalently nor non-covalently linked. This situation is in contrast to the concept of the instant invention. The coexistence of the proteins within the so called virus like particles of Schubert et al. is solely based on the fact that the env proteins are plasma membrane associated proteins. They are localized at the cell surface and, thus, coincidentally they become part of virus like particles by a budding process. The presence of target molecules within virus-like particles of the instant invention is not based on an accidental occurrence. In contrast, it is driven by a highly specific incorporation/encapsulation process of the respective target protein, which results from the use of amino acid sequences which exhibit distinct specific functional properties. One of said amino acid sequences of the signal molecule, i.e the coiled-coil sequence (in former terms the "first amino acid sequence"), interacts specifically in a non-covalent manner with another coiled-coil sequence of a "target molecule". On the other hand, the retroviral capsid sequence (in former terms the "second amino acid sequence of the signal molecule") confers on the signal molecule the ability to assemble into virus like particles. Thus, the methodology described in the instant invention is not based on mere coincidence. The existence of target molecules within virus-like particles of the instant invention is not based on an accidental occurrence. To the contrary, it is due to a highly specific process of incorporation/ encapsulation, due to the use of coiled-coil sequences (see statement above) leading to a strong specific non-covalent interaction between target molecules and signal molecules.

This shows that Schubert et al. only disclose the display of a molecule which serves as an adhesion protein for HIV on the surface of a VSV virus particle. Schubert et al. in particular do not teach:

Attorney Docket No. P66036US1
Appl. No. 09/750,185

1. to use a receptor, i.e., a G-protein coupled receptor, as part of a target molecule, which functions as a receptor and not as an adhesion molecule,
2. to use a retroviral capsid sequence as part of a signal molecule,
3. a method based on a non-covalent interaction between two interacting sequences, and
4. to use coiled-coil sequences as the interacting sequences in 3. above, as being subject matter of the amended independent claims of the present invention.

The examiner is therefore respectfully requested to confirm the novelty of the amended set of claims 237 to 278.

Referenced application EP 0960942 from Van Es et al. discloses a virus-like particle or gene delivery vehicle provided with a ligand capable of binding to a human amino acid transporter. Provided is a ligand capable of binding hCAT1. The amino acid transporter will be present on the cell-surface of the targeted cell. The virus-like particle will be used as a "vector", which will react via its ligand sequence with the respective sequence on the target cell (i.e. the hCAT1) and thus make a fusion of the viral particle and the cell possible. The ligand can be incorporated in the envelope of a retrovirus, or as named by Van Es et al. a virus-like particle, because the retroviral envelope proteins are mutant envelope proteins employing the ligand peptide. Therefore, in the application EP 0960942 the so called virus-like particle is provided with only one molecule, which is a fusion protein of the ligand and the retroviral envelope protein. It is not described how the virus-like particles are generated. No new proteins were introduced into the cells, because the env

Attorney Docket No. P66036US1
Appln. No. 09/750,185

protein, naturally present within the virus, was merely modified. Application EP 09/0942 refers to the use of infectious particles as delivery vehicles.

Thus, the fundamental concept of the present invention as filed, namely the non-covalent interaction between two expression products within a host cell, which should be incorporated/encapsulated into virus-like particles, is not described. (Please refer to the argumentation to Schubert et al. given above). The patent application from Van Es et al. is cited by the applicant on page 6 of the application as filed. Van Es et al. merely disclose the use of infectious virus particles as gene-transfer delivery vehicles. Van Es et al. in particular do not teach :

1. to use a receptor, i.e., a G-protein coupled receptor, as part of a target molecule,
2. to use a retroviral capsid sequence as part of a signal molecule,
3. a method based on a non-covalent interaction between two interacting sequences, and
4. to use coiled-coil sequences, as the interacting sequences in 3. above, as being subject matter of the amended independent claims of the present invention.

The examiner is therefore respectfully requested to confirm the novelty of the amended set of claims 237 to 278.

The disclosure of Kingsman et al. WO 88/03563 relates to a fusion protein capable of assembling into a particle, whereby said fusion protein comprises a first amino acid sequence derived from a retrotransposon or a retrovirus, which confers on the fusion protein the ability to assemble into particles, and a biologically active second amino acid sequence. Substantially important, said fusion proteins are not interacting non-covalently with each other. In fact, they are not interacting

Attorney Docket No. P66036US1
Appln. No. 09/750,185

with each other at all. (Please refer to the argumentation to Schubert et al. given above). The applicant has already referenced WO 88/03563 of Kingsman et al. on page 8 of the instant application as filed.

The basic concept of the present invention as filed, namely the non-covalent interaction between two expression products within a host cell, which should be incorporated/encapsulated into virus-like particles, is not described.

Kingsman et al. in particular do not teach :

1. to use a receptor, i.e., a G-protein coupled receptor, as part of a target molecule,
2. to use a retroviral capsid sequence as part of a signal molecule
3. a method based on a non-covalent interaction between two interacting sequences, and
4. to use coiled-coil sequences, as the interacting sequences in 3. above, all being subject matter of the amended independent claims of the present invention.

The examiner is therefore respectfully requested to confirm the novelty of the amended set of claims 237 to 278.

The statement of rejection cited the international application WO 98/28004, Gowans et al., which discloses the use of virus-like particles and a method for producing virus-like particles. Said virus-like particle is produced by the coexpression of Hepatitis B surface antigen (HBsAg) and an antigenic polypeptide, fused to at least 19 amino acids of the large protein from Hepatitis D virus (L-HDAg), in the same host cell. Said antigenic fusion protein is packaged into virus-like particles through the interaction of the fused 19 amino acids of L-HDAg with the surface antigen HBsAg. On

Attorney Docket No. P66036US1
Appln. No. 09/750,185

pages 27 and 28 of the referenced application, the inventors indicated that HBsAg has to be coexpressed with the respective HDAg-fusion protein to detect said fusion protein in the cell culture fluid of the infected cells. Hence, the inventors speculated that virus-like particles containing said fusion proteins were secreted from the cells. They are not teaching how the fusion protein will be packaged into the virus-like particles through the interaction of the 19 amino acid moiety with HBsAg, nor are they teaching the basis for said interaction. In addition, the HBsAg is not a fusion protein. This is in contrast to the use of two fusion proteins in the instant invention, i.e., the target molecule, wherein a coiled-coil sequence is fused to a G-protein coupled receptor sequence, and the signal molecule, wherein a coiled-coil sequence is fused to a retroviral capsid sequence. These two fusion proteins interact in a non-covalent manner through their coiled-coils. Furthermore, in WO 98/28004 there is no indication of a functional cooperation of the HBsAg with said fusion protein in a non-covalent manner. The applicant has referenced said patent application WO 98/28004 on page 7 of the instant application as filed.

Gowans et al. merely disclose the production of virus like particles containing one fusion protein. The generation of viral-like particles is not described, nor is there any description of how the process of the assembly of a virus-like particle using said molecules will be effected, except taking the conventional way of covalently linking a target molecule and a signal molecule, which fundamentally differs from the approach of the instant invention. Gowans et al. in particular do not teach:

1. to use a receptor, i.e., a G-protein coupled receptor, as part of a target molecule,

Attorney Docket No. P66036US1
Appln. No. 09/750,185

2. to use a retroviral capsid sequence as part of a signal molecule,
3. a method based on a non-covalent interaction between interacting sequences, and
4. to use coiled-coil sequences, as the interacting sequences in 3. above, as being subject matter of the amended independent claims of the present invention.

For the foregoing reasons, none of the references cited in the rejections of record under 35 USC 102(b) anticipates any of the present claims. As such, the rejections of record under 35 USC 102(b) are not applicable against present claims 237 to 278.

With respect to the rejection under §103(a), according to the Office Action, claims 213-231 are rejected as allegedly having been obvious based on the combined teachings of Kingsman et al., Chackerian et al. (P.N.A.S. USA., 1999, 96: 2373-2378), and Tripet et al.

To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art." *In re Wilson*, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970). A "ground of rejection is simply inadequate on its face . . . [when] the cited references do not support each limitation of [the] claim." *In re Thrift*, 63 USPQ2d 2002, 2008 (Fed. Cir. 2002). When conducting an obviousness analysis, "all limitations of a claim must be considered in determining the claimed subject matter as is referred to in 35 U.S.C. 103 and it is error to ignore specific limitations distinguishing over the [prior art] reference." *Ex parte Murphy*, 217 USPQ 479, 481 (PO Bd. App. 1982).

Attorney Docket No. P66036US1
Appln. No. 09/750,185

Kingsman et al. provide a fusion protein or a plurality of fusion proteins each composed of a first and a second amino acid sequence expressed in a single reading frame and being capable to form particles. All fusion proteins have an identical first amino acid sequence. The fusion proteins exist independently from each other and they are not interacting with each other at all. Thus, Kingsman et al. do not teach us to use fusion proteins which are different from each other in their first as well as in their second amino acid sequence, and which are interacting with each other via a non-covalent interaction by specialized interacting sequences. As the method of Kingsman et al. works, it does not provide an incentive for establishing a new and different method.

The same applies to Chackerian et al. who neither teach the use of interacting sequences leading to a non-covalent binding between different fusion protein nor the use of multiple fusion proteins in one system. In addition, they do not teach a method using a retroviral capsid sequence.

Tripet et al. teach to use coiled-coil sequences for the purposes of affinity purification, detection, or immobilization. They designed a protein tag system using said interacting sequences and evidenced its binding interactions and specificities. This tagging system is developed by protein engineers in the light of protein de novo design and engineering techniques, employing it in a rather mechanical context. For instance, they teach us to recover the fusion tags and peptides by chemical removal and/or by immobilization onto affinity matrix columns or onto microchip surfaces. But no information, even not in the least an indication for using said tags, i.e., said coiled coils, in a biological system with virus like particles is given by Tripet et al.. Vice versa, all other publications in some way concerned with virus like particles or the like, see references above, do not teach us at

Attorney Docket No. P66036US1
Appln. No. 09/750,185

all to employ accurately defined non-covalently interacting sequences, i.e., coiled-coil sequences, to induce the incorporation or encapsulation of target molecules in said virus like particles.

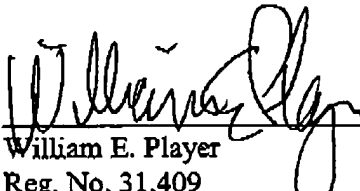
Thus, it would not have been obvious to one skilled in the art from Kingsman et al., Chackerian et al., and Tripet et al., either alone or in combination, to use the engineered coiled-coil sequences in combination with a viral system as presently claimed. Therefore, the present claims are not subject to the rejection of record under 35 USC 103(a).

Favorable action is requested.

Respectfully submitted,

JACOBSON HOLMAN PLLC

By


William E. Player
Reg. No. 31,409

RECEIVED
CENTRAL FAX CENTER
OCT 16 2003

400 Seventh Street, NW
The Jenifer Building
Washington, D.C. 20004
Tel. (202) 638-6666
Fax (202) 393-5350
Date: October 15, 2003
WEP/bap

R:\rthomas\2003\OCTOBER\P66036US1 and.wpd

OFFICIAL